







UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

BERDEEN PROVING GROUND. MD 21018

JOPICAL HAZARD EVALUATION BROGRAM OF CANDIDATE

INSECT REPELLENTS AI3-37135 AND AI3-37156 AND AI3-37157
1.2,3,6-JETRAHYDRO-I-(2-METHYL-1-DYOPENTYL) PYRIDINE,
1-(1-DXOBUTYL)-4-(PHENYLMETHYL) PIPERIDINE, AND
1-(2-METHYL-1-DXOPROPYL-4-(PHENYLMETHYL) PIPERIDINE,
STUDY NOS. 75-51-0020-80, 75-51-0021-80, AND 75-51-0022-80

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CPT Singer/cf/AUTOVON DEPARTMENT OF THE ARMY 584-3980 U.S. ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GROUND, MARYLAND 21010

HSE-LT-T/WP

1 8 JUL 1980

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents,

AI3-37135, AI3-37156, and AI3-37157, 1,2,3,6-Tetrahydro-1-(2methyl-1-oxopentyl) pyridine, 1-(1-oxobutyl)-4-(phenylmethyl) piperidine, and 1-(2-methyl-1-oxopropyl)-4-(phenylmethyl) piperidine, Study Nos. 75-51-0020-80, 75-51-0021-80, and

75-51-0022-80, March 1977 - April 1980

Executive Secretary Armed Forces Pest Management Board Forest Glen Section, WRAMC Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed report follows:

Preliminary hazard evaluations of AI3-37135, AI3-37156, and AI3-37157 were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade compounds did not cause any skin or sensitization reactions, and only mild corneal irritations. AI3-37135 and AI3-37156, however, caused phototoxic reactions, and were not approved for further testing. AI3-37157 did not cause such a reaction, was not acutely toxic by ingestion, and was approved for further testing as a candidate repellent.

FOR THE COMMANDER:

1 Incl as (5 cy) JOHN F MAJ, MSC

Director, Laboratory Services

HQDA (DASG-PSP)

Cdr, HSC (HSPA-P)

Dir. Advisory Ctr on Tox. NRC

Supt, AHS (HSA-IPM)
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DEPARTMENT OF THE ARMY U.S. ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GROUND, MARYLAND 21010

HSE-LT-T/WP

TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENTS AI3-37135, AI3-37156 AND AI3-37157 1,2,3,6-TETRAHYDRO-1-(2-METHYL-1-OXOPENTYL) PYRIDINE, 1-(1-OXOBUTYL)-4-(PHENYLMETHYL) PIPERIDINE, AND 1-(2-METHYL-1-OXOPROPYL-4-(PHENYLMETHYL) PIPERIDINE STUDY NOS. 75-51-0020-80, 75-51-0021-80, AND 75-51-0022-80 MARCH 1977 - APRIL 1980

1. AUTHORITY.

- a. Letter, US Department of Agriculture Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, Florida, 2 March 1977.
- b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of The Surgion General; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration, titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.
- 2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), 1972, revised 1976.
- 3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-37135, AI3-37156 and AI3-37157.
- 4. SUMMARY OF FINDINGS. Hazard evaluations of the above candidate repellents were conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for skin sensitization studies and Sprague-Dawley rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:*t

Approved for public release; distribution unlimited.

^{*} In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1978.

t The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

Study Nos. 75-51-0020-80, 75-51-0021-80, and 75-51-0022-80, Mar 77 - Apr 80

TABLE. PRESENTATION OF DATA

Task	Results	Interpretation
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SKIN IRRITATION STUDIES

Rabbits

Single 24-hour application to intact and abraded skin of New Zealand White rabbits.

None of the three compounds caused any irritation of the intact skin or of the skin surrounding an abrasion.

USAEHA Category I (ref Appendix).

0.5 mL of each technical grade compound applied to each of six rabbits.

EYE IRRITATION STUDIES

Rabbits

Single 24-hour application of 0.1 mL of each technical caused mild irritation of grade compound to one eye of corneal and conjunctival each of six New Zealand White rabbits.

All of the three compounds USAEHA Category C tissues.

(ref Appendix).

APPROXIMATE LETHAL DOSE (ALD)

Oral

Rats (male) - no diluent

The ALD for AI3-37156 was determined to be >7400 mg/kg.

Neither AI3-37156 or AI3-37157 presents a lethal hazard from accidental ingestion.

The ALD for AI3-37157 was found to be 3300 mg/kg.

AI3-37135 was not tested for ALD.

Test

Results

Interpretation

PHOTOCHEMICAL SKIN IRRITATION STUDIES

Rabbits

A single 0.05 mL application of a 25 percent (w/v) solution of each compound and a 10 percent (w/v) 0il of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to UV light (355 nm) for 30 minutes at a distance of 10-15 cm.

A 25 percent solution of both Al3-37135 and Al3-37156 in ethanol caused a photochemical irritation reaction. Al3-37157 did not cause such reaction. Compounds AI3-37135 and AI3-37156 caused a photochemical irritation reaction under test conditions and may cause a similar photochemical irritation in humans.

Compound AI3-37157 would not be expected to cause a phototoxic reaction in humans.

Control

Following UV exposures of the rabbits, 0.05 mL of test compounds, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48 and 72 hours.

Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.

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Test

Results

Interpretation

SENSITIZATION STUDIES

Guinea Pigs (Male)

Intradermal injections of 0.1 mL of a 0.1 percent solution (w/v) of each compound or of dinitro-chlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.

Ten test guinea pigs were given 10 sensitizing doses of each compound over a 3-week period. After 2 weeks rest, they were challenged with ID injections of each respective test compound.

Ten positive control guinea pigs were sensitized over 3 weeks with DNCB.
After 2 weeks rest, they were challenged with ID injections of DNCB.

Challenge dose of all compounds did not produce sensitization reactions.

Challenge doses of DNCB in positive control guinea pigs produces a marked sensitization reaction in 10 out of 10 guinea pigs.

Compounds AI3-37135, AI3-37156 and AI3-37157 did not produce sensitization reactions under test conditions and are not expected to produce sensitization reactions in man.

DNCB produced a marked reaction, indicating the guinea pigs respond to sensitizing agents.

^{*} A known skin sensitizer

^{5.} CONCLUSION. Compounds AI3-37135 and AI3-37156 in ethanol caused phototoxic reactions in rabbits and may cause similar reactions in man. Compound AI3-37157 caused no such reaction, nor any primary skin irritation or skin sensitization. While mildly irritating to ocular tissues, AI3-37157 was not acutely toxic by ingestion.

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6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37157 be approved for further testing as a candidate insect repellent. Compounds AI3-37135 and AI3-37156 cannot be classed as nonhazardous, and it is recommended that they be disapproved for further testing.

ALLEN W. SINGER
CPT, VC
Laboratory Animal Veterinary Officer
Toxicology Division

APPROVED:

ARTHUR H. McCREESH, Ph.D. Chief, Toxicology Division Study Nos. 75-51-0020-80, 75-51-0021-80, and 75-51-0022-80, Mar 77 - Apr 80 APPENDIX

TOPICAL HAZARD EVALUATION PROGRAM DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING CONSIDERED FOR ACUTE SKIN APPLICATION

<u>CATEGORY I</u> - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

<u>CATEGORY II</u> - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound.

(INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

- A. <u>Compounds noninjurious to the eye</u>. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.
- B. <u>Compounds producing mild injury to the cornea</u>. INTERPRETATION: Should be used with caution around the eyes.
- C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.
- D. <u>Compounds producing moderate injury to the cornea</u>. INTERPRETATION: Should be used with extreme caution around the eyes.
- E. <u>Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva</u>. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.
- F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.